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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/602,351	06/23/2000	Barbara K. Finck	2945-A	1329

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EXAMINER	
ROMEO, DAVID S	
ART UNIT	**PAPER NUMBER**
1647	28

DATE MAILED: 05/05/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/602,351	Applicant(s) FINCK ET AL.	
	Examiner David S Romeo	Art Unit 1647	

-- Th MAILING DATE of this communication appears on the cover sh et with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 February 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-6,8 and 11-23* is/are pending in the application.

4a) Of the above claim(s) *14-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-6,8,11-13 and 19-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1,3-6,8 and 11-23* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *17* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment filed October 28, 2002 (Paper No. 15) has been entered. Claims 1, 3-6, 8, 11-23 are pending. Applicant's elected without traverse group II, claim(s) 1-13, to the extent that they are drawn to a method of treating ordinary psoriasis comprising administering TNFR:Fc, in Paper No. 11. Claims 14-18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 11. The examiner called Ms. Sheiness on April 11, 2002 to request an election of species as set forth in the restriction requirement mailed October 1, 2001 (Paper No. 7). In response Ms. Sheiness elected without traverse the species "psoralen combined with ultraviolet light A" for prosecution on the merits. See the interview summary attached to the Office action mailed April 22, 2002 (Paper No. 13).

Applicant's election of the species plaque psoriasis in Paper No. 19 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1, 3-6, 8, 11-13, 19-23 are being examined to the extent that they read upon a method of treating plaque psoriasis by administering TNFR:Fc in combination with "psoralen combined with ultraviolet light A."

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Citations by the examiner are in an alphanumeric format, such as "(a1)", wherein the "a" refers to the reference cited on the Notice of References Cited, PTO-892, and the "1" refers to the Paper No. to which the Notice of References Cited, PTO-892, is attached.

Maintained Formal Matters, Objections, and/or Rejections:

Claim Rejections - 35 USC § 103

Claims 1, 3-6, 12, 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barnes (u13), Moreland (v13), Mandell (U.S. Patent No. 4965271, cited by Applicants), and Jacobs (U.S. Patent No. 5605690, cited by Applicants).

In addition, the examiner relies upon Gilhar (1996, cited by Applicants).

The rejection of record is applied to claims 22, 23.

In addition, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to establish a baseline in an indicator selected from the group consisting of psoriasis area and severity index (PASI) and Target Lesion Assessment Score within 60 days of administering the first dose, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to establish such an indicator so the effect of the treatment could be objectively evaluated and modified if necessary. The invention is prima facie obvious over the prior art.

Applicant argues that Barnes does not teach that psoriasis can be treated by inhibiting TNF-α and that Barnes suggests that to treat psoriasis several different cytokines might need to be inhibited. Applicant's arguments have been fully considered but they are not persuasive.

Regarding the former, Barnes does teach that that in chronic inflammatory diseases, such as psoriasis, several cytokines recruit activated immune and inflammatory cells to the site of lesions, thereby amplifying and perpetuating the inflammatory state. The production of TNF-α is increased in patients with psoriasis and TNF-α has an important role in the inflammatory process. Barnes clearly and specifically suggest that elevated levels of TNF-α play a role in the psoriasis, which provides a specific suggestion to treat psoriasis by inhibiting TNF-α. Implicit in the latter argument is that Barnes does suggest treatment of psoriasis by neutralizing TNF-α, and the present claims encompass the neutralization of TNF-α with the neutralization of any and all other molecules. The claims are not limited to the sole administration of TNFR:Fc. Rather, because the claims use open, i.e., comprising, language the claims encompass the administration not only TNFR:Fc, but also the administration of TNFR:Fc in combination with any and all other treatments.

Applicant argues that Moreland does not mention psoriasis and does not suggest that diseases other than rheumatoid arthritis should be treated with TNFR:Fc. Applicant's arguments have been fully considered but they are not persuasive. Moreland does teach the antagonism of TNF with TNFR:Fc in a diseases in which TNF is involved.

Applicant argues that Mandell does not teach or suggest that one should substitute xanthine compounds for other therapeutic agents, that one following Mandell's teachings would not expect TNFR:Fc to be successful, and that Mandell teaches away from such a substitution. Applicant's arguments have been fully considered but they are not persuasive. Mandell teaches that psoriasis is among the conditions that can be treated or alleviated by the inhibition of IL-1, TNF, and other leukocyte derived cytokines, which is a specific suggestion to one of ordinary

skill in the art to treat psoriasis by inhibiting TNF-α. It is also noted that Barnes (u13) teaches that in chronic inflammatory diseases, such as rheumatoid arthritis, several cytokines recruit activated immune and inflammatory cells to the site of lesions, thereby amplifying and perpetuating the inflammatory state, and that the treatment of patients with rheumatoid arthritis with antibodies to the single cytokine TNF-α can control refractory disease. See page 1067, paragraph bridging left and right columns. In other words, there is a reasonable expectation that even though several cytokines recruit activated immune and inflammatory cells to the site of lesions the inhibition of TNF-α can control refractory disease.

Applicant argues that Jacobs does not mention psoriasis. Applicant's arguments have been fully considered but they are not persuasive. Jacobs does teach that the amount and frequency of administration of a TNF-α antagonist will depend, of course, on such factors as the nature and severity of the indication being treated, the desired response, the condition of the patient, and so forth.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on

combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant argues that Creaven and Takematsu teach away from the present invention and that the results of the present method are unexpected. Applicant's arguments have been fully considered but they are not persuasive. Creaven and Takematsu do not teach that psoriasis cannot be treated by inhibiting TNF-α. Furthermore, Gilhar teaches that supraphysiological levels of TNF-alpha may saturate and consequently down-regulate their own receptors, leading to a paradoxical inhibitory effect (Abstract). Gilhar is evidence that the results of Creaven and Takematsu are consistent with the suggestion to treat psoriasis by inhibiting TNF-α of the cited references in the present rejection. Gilhar is also evidence that the results of the present method are not unexpected.

Claims 1, 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barnes (u13), Moreland (v13), Mandell (U.S. Patent No. 4965271, cited by Applicants), and Jacobs (U.S. Patent No. 5605690, cited by Applicants) as applied to claim 1 above, and further in view of Wallach (a13, U.S. Patent No. 6083534).

In addition, the examiner relies upon Gilhar (1996, cited by Applicants).

Applicants paraphrase their arguments made in response to the previous rejection and these arguments have been fully considered but they are not persuasive for the reasons discussed above.

Applicant argues that Wallach provides no motivation to combine Wallach's teachings with Barnes, Moreland, Mandell, and Jacobs, and that Wallach does not teach the treatment of

psoriasis. Applicant's arguments have been fully considered but they are not persuasive. One of ordinary skill in the art would be motivated to combine these teachings because controlled release systems provide advantages over conventional drug therapies.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Claims 1, 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barnes (u13), Moreland (v13), Mandell (U.S. Patent No. 4965271, cited by Applicants), and Jacobs (U.S. Patent No. 5605690, cited by Applicants) as applied to claims 1, 2 above, and further in view of Pamukcu (b13) and Feldman (w13).

In addition, the examiner relies upon Gilhar (1996, cited by Applicants).

Applicant argues that one skilled in the art would not combine PUVA with TNFR:Fc without knowing that TNFR:Fc is a suitable treatment for psoriasis, and that Pamukcu does not mention TNF-α. Applicant's arguments have been fully considered but they are not persuasive. Implicit in this argument is that if treatment of psoriasis with TNFR:Fc is obvious then it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to combine PUVA with TNFR:Fc. The treatment of psoriasis with TNFR:Fc is prima facie obvious. Pamukcu also teaches that photochemotherapy (PUVA) (an acronym for the combination of the drug Psoralen with Ultraviolet A Light) can also be combined with other psoriasis therapies. See column 2, full paragraph 5. Pamukcu clearly suggests combing

photochemotherapy with other therapies. The combination of PUVA with TNFR:Fc is prima facie obvious in the absence of evidence to the contrary.

Applicant argues that Feldman does not mention psoriasis and sheds no light on the pathway of psoriasis. Applicant's arguments have been fully considered but they are not persuasive. Barnes (u13) teaches that psoriasis is a chronic inflammatory disease and Feldman teaches that the most effective therapy in immune inflammatory diseases will come from therapy aimed at several points in the disease pathway. Such combination therapies, if given early in the course of the disease process, may be able to control the disease.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

New formal matters, objections, and/or rejections:

Inventorship

In view of the papers filed October 28, 2002 (Paper No. 16), the inventorship in this nonprovisional application has been changed by the deletion of Larry O'Neal, John D. Pluenneke, and Timothy Connor.

The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of the file jacket and PTO PALM data to reflect the inventorship as corrected.

Claim Rejections - 35 USC § 112

Claims 3, 22, 23 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 3, 22, 23 are indefinite because it is unclear if the baseline value is established before or after the first dose. The metes and bounds are not clearly set forth. It is suggested that the claims recite "within 60 days prior to administering the first dose."

Priority

The subject matter of claims 19-21 is not entitled to the benefit of the filing dates of any of the earlier filed applications for which benefit is claimed because the subject matter of claims 19-21 is not disclosed in the manner provided by 35 U.S.C. 112, first paragraph, in the earlier filed applications. Accordingly, the subject matter defined in claims 19-21 has an effective filing date of June 23, 2000, the filing date of the present application. Should applicant disagree, it is incumbent upon applicant to provide the serial number and specific page number(s) of any parent application filed prior to June 23, 2000 which specifically supports claims 19-21 and which applicant considers to have been in possession of and fully enabled for prior to June 23, 2000.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 19 is rejected under 35 U.S.C. 102(a) as being anticipated by Bundow (1999, cited by Applicants). Bundow discloses a method of treating a human patient having psoriatic plaques comprising administering etanercept to said patient. The psoriatic rash improved dramatically, indicating the amount of etanercept administered was a therapeutically effective amount. The fact that the patient had psoriatic plaques indicates that the patient had plaque psoriasis.

Claim Rejections - 35 USC § 103

Claims 1, 12, 13, 19-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barnes (u13), Moreland (v13), Mandell (U.S. Patent No. 4965271, cited by Applicants), Jacobs (U.S. Patent No. 5605690, cited by Applicants), and Gilhar (1996, cited by Applicants) as applied to claims 1, 12, 13 above and further in view of Ettahadi (1994) or {Ettahadi (1994) in view of Bundow (1999, cited by Applicants)}.

Barnes, Moreland, Mandell, and Jacobs teach the administration of TNFR:Fc for the treatment of psoriasis, as discussed above. Barnes, Moreland, Mandell, and Jacobs are silent with respect to the treatment of plaque psoriasis.

Ettahadi teaches that levels of TNF-α are elevated in psoriatic skin lesions (Abstract) from patients with chronic plaque psoriasis (page 147, left column, full paragraph 1). Ettahadi does not teach treating plaque psoriasis by administering TNFR:Fc.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to administer TNFR:Fc for the treatment of psoriasis, as taught by Barnes, Moreland, Mandell, and Jacobs, and to modify that teaching by administering TNFR:Fc for the

treatment of plaque psoriasis with a reasonable expectation of success. One of ordinary skill in the art would be motivated to combine these teachings because in chronic inflammatory diseases, such as psoriasis, several cytokines recruit activated immune and inflammatory cells to the site of lesions, thereby amplifying and perpetuating the inflammatory state. The production of TNF-α is increased in patients with psoriasis and TNF-α has an important role in the inflammatory process and the levels of TNF-α are elevated in psoriatic skin lesions from patients with chronic plaque psoriasis. The invention is prima facie obvious over the prior art.

Alternatively, Ettahadi teaches that levels of TNF-α are elevated in psoriatic skin lesions (Abstract) from patients with chronic plaque psoriasis (page 147, left column, full paragraph 1). Ettahadi does not teach treating plaque psoriasis by administering TNFR:Fc.

Bundow discloses a method of treating a human patient having psoriatic plaques comprising administering etanercept to said patient. The psoriatic rash improved dramatically, indicating the amount of etanercept administered was a therapeutically effective amount. The fact that the patient had psoriatic plaques indicates that the patient had plaque psoriasis. Bundow does not teach treating a pediatric patient or ~~andult~~ an adult patient with the amounts and frequency of TNFR:Fc indicated in claims 12, 13.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to administer TNFR:Fc for the treatment of psoriasis with the amounts and frequency of TNFR:Fc indicated in claims 12, 13, as taught by Barnes, Moreland, Mandell, and Jacobs, and to modify that teaching by administering TNFR:Fc for the treatment of plaque psoriasis with a reasonable expectation of success. One of ordinary skill in the art would be motivated to combine these teachings because in chronic inflammatory diseases, such as

psoriasis, several cytokines recruit activated immune and inflammatory cells to the site of lesions, thereby amplifying and perpetuating the inflammatory state. The production of TNF-α is increased in patients with psoriasis and TNF-α has an important role in the inflammatory process and the levels of TNF-α are elevated in psoriatic skin lesions from patients with chronic plaque psoriasis. The invention is prima facie obvious over the prior art. Bundow is further evidence of a reasonable expectation of success.

Conclusion

No claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (703) 305-4050. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 7:30 A.M. TO 4:00 P.M.

IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, GARY KUNZ, CAN BE REACHED ON (703) 308-4623.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE FOLLOWING TC 1600 BEFORE AND AFTER FINAL RIGHTFAX NUMBERS:

BEFORE FINAL (703) 872-9306
AFTER FINAL (703) 872-9307

IN ADDITION TO THE OFFICIAL RIGHTFAX NUMBERS ABOVE, THE TC 1600 FAX CENTER HAS THE FOLLOWING OFFICIAL FAX NUMBERS: (703) 305-3592, (703) 308-4242 AND (703) 305-3014.

CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

FAXED DRAFT OR INFORMAL COMMUNICATIONS SHOULD BE DIRECTED TO THE EXAMINER AT (703) 308-0294.

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.

DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

DSR
MAY 1, 2003